Direct Visualization of Superdisintegrant Hydration Using Environmental Scanning Electron Microscopy

To the Editor:

The mechanisms of action of pharmaceutical superdisintegrants have been studied by many groups over the last decade, and swelling and wicking of water have been proposed as their primary modes of action.[1-3] Both the extent and rate of disintegrant swelling upon immersion in water have been related to tablet disintegration,[4] but neither of these factors appears to be uniquely responsible for the disintegration process. Disintegrating force development has also been proposed as a factor, and the efficiency of some superdisintegrants may be related to their high rate of water uptake through a wicking mechanism.[5] The hydration of superdisintegrants has been studied using techniques such as optical microscopy,[6,7] electrical zone sensing (Coulter counter),[8] and video recording.[9] Each of these techniques involves examining the particles under some form of constraint (*e.g.*, ionic strength for the Coulter counter and mechanical constraint (a glass cover slide) for optical microscopy and video recording). These constraints may alter the hydration behavior of the disintegrant particles when exposed to an aqueous environment. In order to minimize the effects of such constraints we have directly observed the hydration behavior of several superdisintegrant powders using an environmental scanning electron microscope (ESEM). The results of these studies are described in this Communication.

Three types of superdisintegrant were investigated, croscarmellose sodium (Ac-Di-Sol, FMC Corp.), crospovidone (Kollidon CL, BASF Corp.), and sodium starch glycolate (Explotab, Edward Mendell Co., Inc.), and each was used as received. Sodium chloride (analytical grade) and microcrystalline cellulose (Avicel PH101, FMC Corp.) were examined as reference materials.

A calibrated dynamic moisture balance (MB-300G, VTI Corp., Hialeah, FL) was used to evaluate the moisture sorption characteristics of the materials at a range of relative humidities. A conventional scanning electron microscope (SEM) (JSM-820, Jeol Corp., Peabody, MA) was used for preliminary observation of the superdisintegrants. An Oxford Cryostage (model Cryotrans, Oxford Instruments, Oxford, U.K.) attached to a side port of the JSM-820 was used for cryo-SEM studies of the materials. An ESEM (model 2010, ElectroScan Corp., Wilmington, MA) was used to observe the superdisintegrants when exposed to controlled amounts of water vapor. This instrument allows visualization of samples without the usual coating procedure associated with standard SEM, and under varying water vapor pressures. The principles used in the imaging of the materials are similar to those of conventional SEM. The difference lies in the use of a differential-vacuum pumping system and pressure-limiting orifices to create a controlled-pressure water vapor environment. Before the ESEM experiments were started, the accuracy of the relative humidity (RH) control in the chamber was tested by observation of the deliquescence of sodium chloride crystals. This occurred at about 8.8 Torr, which corresponds to 70% RH at 15 °C (Figure 1). This is close to the reported literature value of 75% RH and confirms the accurate control of water vapor pressure and temperature in the ESEM chamber.

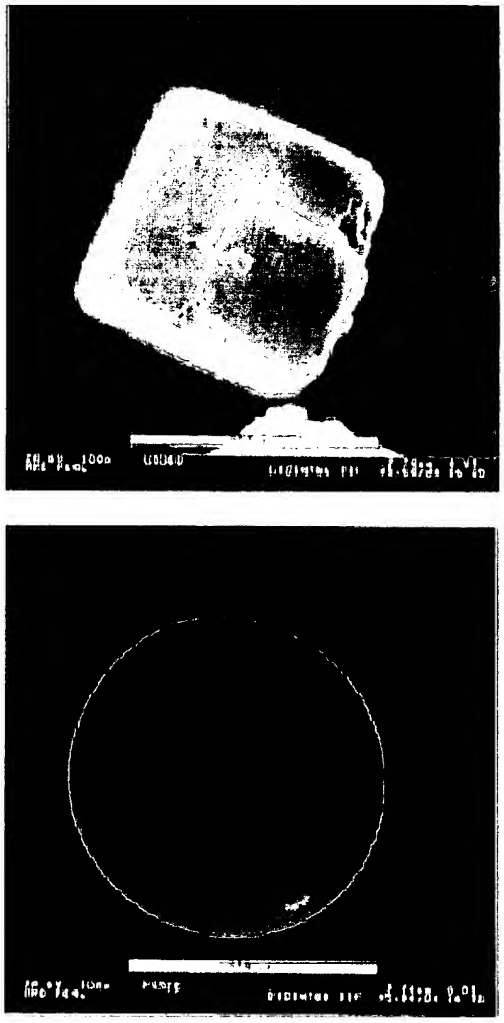

Figure 1—Sodium chloride crystal (a, top) initially at 40% RH/15 °C and (b, bottom) undergoing deliquescence at 75%RH/15 °C.

The dynamic water vapor sorption experiments indicated that the maximum amount of water vapor sorbed at 90% RH for the different superdisintegrant samples varied between 48% w/w for croscarmellose sodium to 62% w/w for sodium starch glycolate (Figure 2a–c). Sodium starch glycolate and crospovidone showed minimal hysteresis in their water vapor sorption–desorption curves, as opposed to a marked hysteresis observed for the croscarmellose sodium sample. There was no evidence of macroscopic morphological changes in any of the specimens during or after the water vapor sorption experiments, except for a worsening of the flow properties of the powders stored at high humidity.

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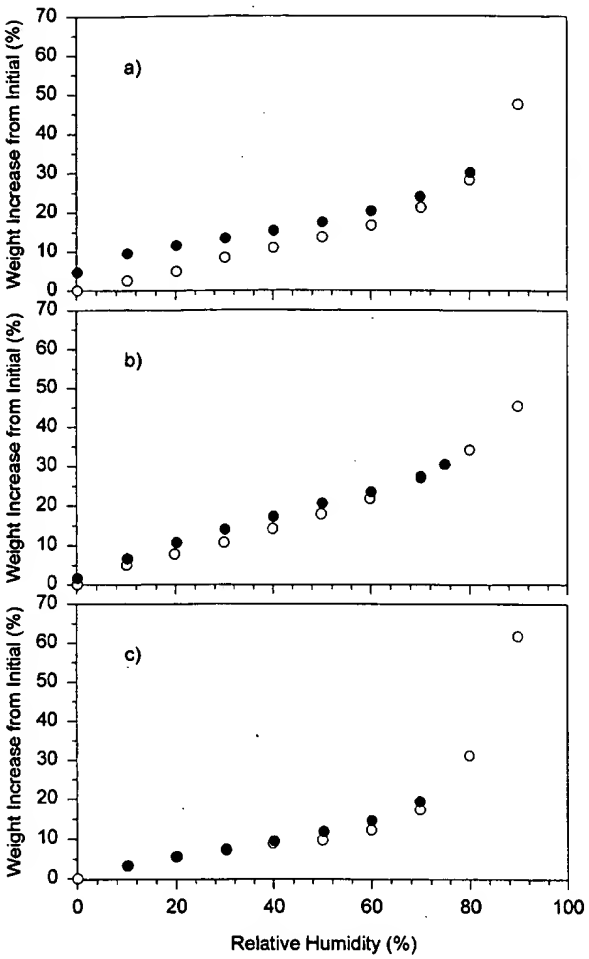

Figure 2—The water vapor sorption (○) and desorption (●) isotherms for (a) croscarmellose sodium, (b) crospovidone, and (c) sodium starch glycolate.

Several samples of the superdisintegrants were equilibrated at a relative humidity of 92% RH at 30 °C (using a saturated solution of potassium nitrate in a desiccator) for a period of 1 week and examined by conventional SEM and cryo-SEM. There were no noticeable differences in the morphology andstructure of these samples compared to similar samples stored under ambient conditions. The lack of any morphological differences after storage at high relative humidities was unexpected[5,9] and inconsistent with the observed water vapor sorption behavior. If water was placed directly on the samples, followed by rapid freezing in the cryo-SEM, morphological and surface changes were observed for all three superdisintegrants. These included swelling, untwisting, and fusion of the particles (not shown). This illustrates some of the problems associated with using conventional high-vacuum SEM methods for observing hydrated pharmaceutical materials. It appears that dehydration of samples in a regular SEM can be very rapid, even under low temperature (cryogenic) conditions, and this can prevent direct observation of hydrated specimens.

Direct visualization of the hydration behavior of the superdisintegrants was made by observing uncoated samples in the ESEM. The water vapor pressure was initially set at 4.9 Torr, which corresponds to a relative humidity of approximately 40% at 15 °C. The samples were allowed 5 min to equilibrate in this environment. The water vapor pressure was then increased gradually to 10 torr (80% RH at 15 °C), and the samples were allowed 5 min to equilibrate. The last step was to slowly lower the relative water vapor pressure back to 4.9 Torr to partially dehydrate the samples. This range of relative humidities was chosen to represent the likely humidities experienced by the superdisintegrants during normal pharmaceutical storage and processing operations. At 40% RH the croscarmellose sodium particles comprised twisted fibers approximately 180 μm in length and 25 μm in diameter (Figure 3a). Upon exposure to 80% RH the particles experienced considerable twisting and expansion (Figure 3b). These modifications were visualized in real time as the relative humidity in the chamber increased. After the relative humidity was reduced to 40%, the particles did not regain their original shape (Figure 3c), and this may be linked to the hysteresis observed in the water vapor sorption isotherm for this material (Figure 2a). The sodium starch glycolate particles initially comprised oblate particles approximately 40 μm in diameter (Figure 4a). Upon exposure to an elevated relative humidity (80% RH) the particles experienced swelling and deformation (Figure 4b). Fusion of particles was also observed, and this caused irreversible changes in the structure of the material even after reduction of the relative humidity to 40%. Some shrinkage of the fused material was observed on dehydration/drying (Figure 4c). In contrast to the croscarmellose, the water vapor sorption isotherm for the sodium starch glycolate showed no sorption–desorption hysteresis over this range of relative humidities (Figure 2b) despite the obvious structural changes that were taking place in the sample. In the case of crospovidone, the material comprised highly tortuous particles resembling crumpled pieces of paper as previously reported.[10] There were very few signs of swelling even after prolonged exposure to 80% RH, and the particles maintained their physical integrity upon dehydration and repeated hydration–dehydration cycling (not shown). The surface aspects and morphology of the particles were not noticeably changed even when observed at high magnification. The effect of changing relative humidity on the morphology of particles of microcrystalline cellulose, a widely used pharmaceutical tabletting excipient, was also determined. There were no observable changes in the particle morphology nor was there any swelling of the microcrystalline cellulose particles after prolonged exposure to a relative humidity of 80%. These results are consistent with the limited disintegrant properties of this material[10] and its lower reported level of water vapor sorption.[11]

Conclusions—The morphological properties of pharmaceutical materials in their near native states can be readily determined as a function of relative humidity and temperature using environmental scanning electron microscopy. Other advantages of ESEM include greater resolution, increased depth of field, and higher magnification compared to light microscopy, and the lack of the potentially destructive sample preparation techniques required for conventional SEM observation. ESEM has been used to directly observe the hydration behavior of several materials used as superdisintegrants in pharmaceutical tablet formulations. The technique provided direct visual confirmation of the importance of swelling as a mechanism of action for two commercially available superdisintegrants, croscarmellose sodium and sodium starch glycolate. Additionally, it indicated that crospovidone does not undergo any large degree of swelling during hydration in its native state. Other modes of action (*e.g.*, wicking) could not be directly confirmed; however, it was

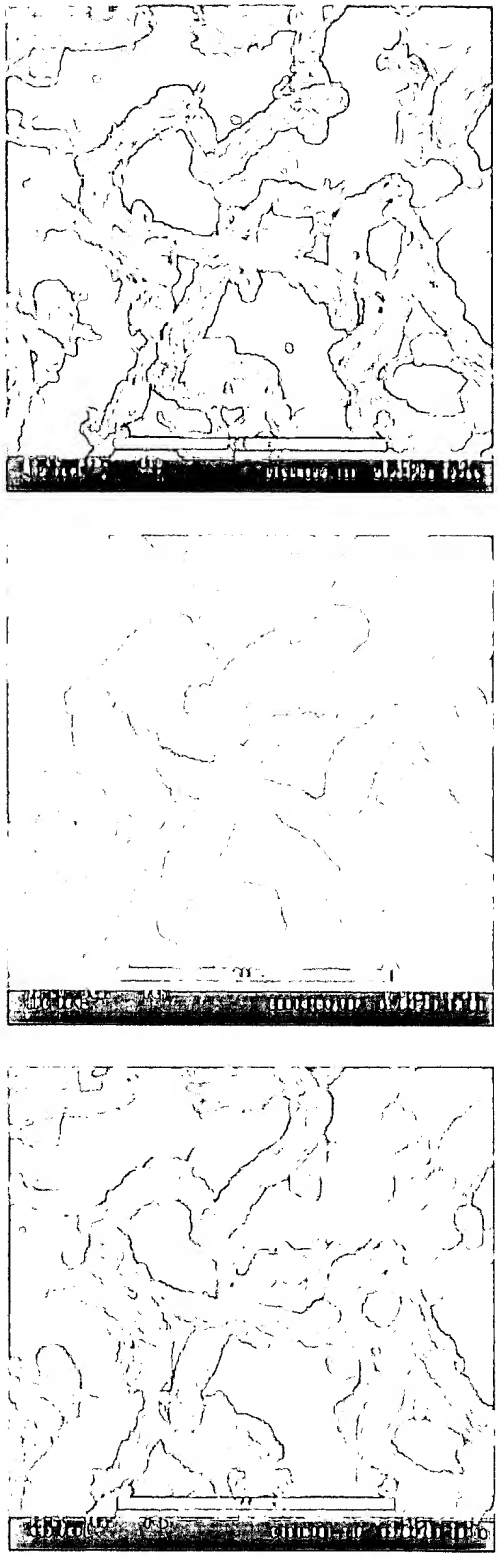

Figure 3—Croscarmellose sodium particles (a, top) at 40% RH/15 °C, (b, middle) at 80% RH/15 °C, and (c, bottom) after "drying" at 40% RH/15 °C.

Figure 4—Sodium starch glycolate particles undergoing hydration (a, top) at 40% RH/15 °C, (b, middle) at 80% RH/15 °C, and (c, bottom) after "drying" at 40% RH/15 °C.

observed that the morphological changes for each material were unique, suggesting different modes of superdisintegrant action for each excipient. Following this initial feasibility study we plan to develop image analysis techniques to quantify the morphological changes that have been observed and to study the effects of processing (*e.g.*, compression, milling) on the hydration behavior of pharmaceutical superdisintegrants.

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